CASE REPORT

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Lupus Glomerulonephritis in a Patient with Primary Sjögren's Syndrome

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ABSTRACT Primary Sjögren's syndrome (pSS) is a chronic inflammatory autoimmune disease that can occur in a primary form or assosiated with other systemic diseases such as systemic lupus erythematosus (SLE). Here, we present a patient with diagnosis of pSS who developed lupus nephritis (LN) five years later and had no manifestations of SLE clinically. The urine analysis including proteinuria, leukocyturia and hematuria and hypocomplementemia alerts us of the presence of immunocomplex glomerulonephritis. The histopathological findings of renal biopsy of the patient revealed focal proliferative glomerulonephritis with "full house" immunofluorescence pattern compatible with SLE. Remission was achieved after three months of immunosupression. Despite clinical remission, C4 levels remained low in follow up. This case illustrates the importance of closely follow up of patients with low complement levels developed in the course of pSS.

Keywords: Primary Sjögren's syndrome; lupus nephritis; SLE; hypocomplementemia

Sjögren's syndrome (SS) is an autoimmune disease characterized by lymphocytic infiltration of exocrine glands.[1] The disease presents alone [primary SS (pSS)] or in association with other autoimmune diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (secondary SS). Clinical presentation varies from mild symptoms, such as classical sicca symptoms of dry eyes and dry mouth to severe systemic symptoms, involving multiple organ systems.[1] Development of hypocomplementemia in the course of pSS predict an unfavorable outcomes, including severe renal disease with malign hypertension (HT) and lymphoma. The reduced serum levels of complement commonly due to consumption is well known in SLE and lupus nephritis (LN) and is interpreted as a marker of disease activity. On the other hand, low serum complement levels could be related to genetic deficiency that predisposes to the development of lupus. When hypocomplementemia or severe HT are diagnosed during the course of pSS, vasculitis or glomerulonephritis due to mixed cryoglobulins or immune complex, systemic lupus erythematosus overlapping pSS should be considered.

In this report, we described a case of pSS patient who developed LN and emphasized the importance of complement disorders which are implicated in the pathogenesis of SLE in order to make the accurate diagnosis.

CASE REPORT

A 42-year-old woman was admitted to the hospital with severe shortness of breath. Over the past two months she was referred to the hospital twice with similar complains and she required intensive care admission for life-threatening pulmonary edema during the last hospital visit whereas the cause of pulmonary edema was not defined. The patient had a history of primary hypothyroidism due to autoimmune thyroiditis and pSS, first diagnosed in 2013. Data obtained from the hospital files and her previous rheumatologist revealed that she was under follow up without any extraglandular organ involvement. **Her diagnosis of pSS was made on classical criteria of objective xerophthalmia, recurrent salivary gland swelling, positive autoantibodies against SS-A and histopathologic conformation of lymphocytic infiltrates in minor salivary glands.** Medications included lubricant eye drops, levothyroxine, furosemide. She never used alcohol or tobacco.

On physical examination, patient had dyspnea, diaphoresis and cyanosis of the lips. Arterial blood pressure (ABP) was 220/120 mmHg, heart rate118 beat/min. There was a S4 and grade 2/6 systolic murmur at the cardiac apex. Pulmonary exam was remarkable for bibasiler rales. There was pitting edema in lower extremities.

Complete blood count revealed mild anemia and lymphocytopenia with a normal leukocyte and platelet counts. She had hypoalbuminemia, hyponatremia and high creatinine levels. The acute phase reactants were markedly elevated (Table 1). The patient was negative for hepatitis B and C and human immunodeficiency virus. The cardiac troponins were normal. Urinalysis revealed proteinuria, **leukocyturia** and hematuria. Her electrocardiogram showed sinus tachycardia. Lung X-ray revealed bilateral pleural effusion. A diagnostic thoracentesis revealed transudate. Transthoracic echocardiography showed a preserved ejection fraction, diastolic dysfunction and mild mitral valve regurgitation.

Glyceryl trinitrate and loop diuretic infusion were initiated for treatment of pulmonary edema. Symptoms of dispnea resolved within the same day, however ABP did not decrease efficiently. During the following days urinary output decreased and renal function continued to deteriorate. The patient was considered to have new-onset resistant HT resulting in pulmonary edema that was thougth either to be complicated with or resulting from

TABLE 1: The initial and follow up laboratory data of the patient.

Variables	At admission	On 7th day	At discharge	At 1th months	At 8th months
Leukocyte (10^3/μL)	4.99	6.8	15.6	18.15	10.2
Neutrophil (10^3/μL)	3.7	5.65	13.7	14.2	5.9
Lymphocyte (10^3/μL)	1.04	0.68	0.9	2.8	2.68
Hemoglobin (g/dL)	9.5	8.8	9.6	10.5	13
Platelet (10^3/μL)	232000	243000	238000	383000	272000
C-reactive protein (mg/dL)	69			7.39	4
ESR* (mm/h)	119			45	21
Urea (mg/dL)	103	97	109	103	32
Creatinine (mg/dL)	1.4	3.27	2	1.5	0.9
Na* (mmol/L)	126	123	128	134	136
Albumin (g/dL)	3.2	2.64	2.8	3.3	3.6
Total protein (g/dL)		5.8			6.4
C3 (mg/dL; n: 90-180)		77		117	162
C4 (mg/dL; n: 10-40)		1.69		1.85	7.73
Spot Protein/Creatinine Ratio (mg/d)	3557			789	125

*ESR: erythrocyte sedimentation rate, Na: natrium.

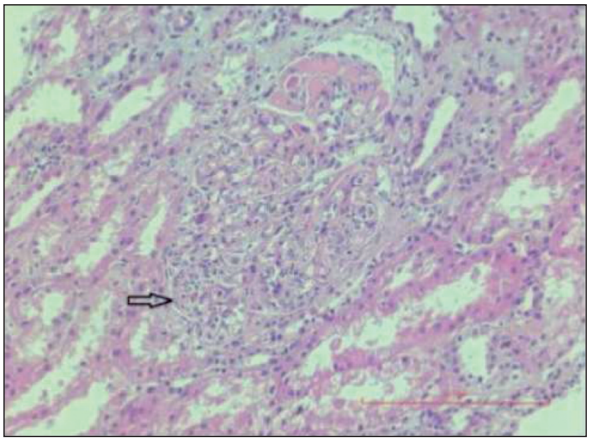

FIGURE 1: Light microscopy showing focal and segmental endocapillary hypercellularity.

acute renal injury. We excluded bilateral renal artery stenosis and endocrine etiology of HT. We performed a renal biopsy and additional serological studies. Anti-nuclear antibodies (1:640, fine speckled), rheumatoid factor 54 IU/mL, and anti-Ro antibodies (3+) were positive, while anti double stranded DNA antibodies (anti ds DNA) and other autoantibodies were negative. Serum complement levels were decreased (Table 1). No cryofibrinogen or cryoglobulin was detected. The renal biopsy revealed focal and segmental endocapillary hypercellularity on light microscopy. Direct immunofluorescence demonstrated "full-house" staining for IgG (2+), IgA (1+), IgM (2+), C1q (2+), and C3 (2+). Smaller numbers of subepithelial and mesangial deposits were also seen. There was evidence of vasculitis in medium or small vessels. A renal biopsy revealed findings **consistent** with focal proliferative glomerulonephritis (Figure 1, Figure 2 a, b, c). We established the diagnosis of class 3 LN and prednisolone (1 mg/kg/day) and mycophenolate mofetil (2 g/daily) therapy were initiated. The patient's condition improved with the initiation of treatment and she was in complete response according to KDIGO criteria after three months. At the 9 months' follow up C4 remained low. Informed Consent: Informed consent were obtained from the patient.

DISCUSSION

In the present case, we described a middle-aged woman who developed LN after establish the diagnosis of pSS. Here we highlighted the factors associated with the development of LN in pSS patients and their importance in making the accurate diagnosis.

The coexistance of pSS and SLE is being reported with rate between 7.5-19%.[2,3] The association of these two diseases first mentioned in 1959 in a study by Heaton where pSS was asserted to be a benign form of SLE. Recent data have suggested that despite pSS and SLE share many critical common dysregulated immune pathways they are two distinct entities.[4] pSS is a disease first and foremost of exocrine glands that generally have a slow course whereas SLE is a entity that affects younger women and characterized by exacerbations and remissions and might lead to serious organ damage.

The development of SLE may precede the diagnosis of pSS by 1-19 years.[2-6] In current case our patient developed SLE five years after being diagnosed with pSS.

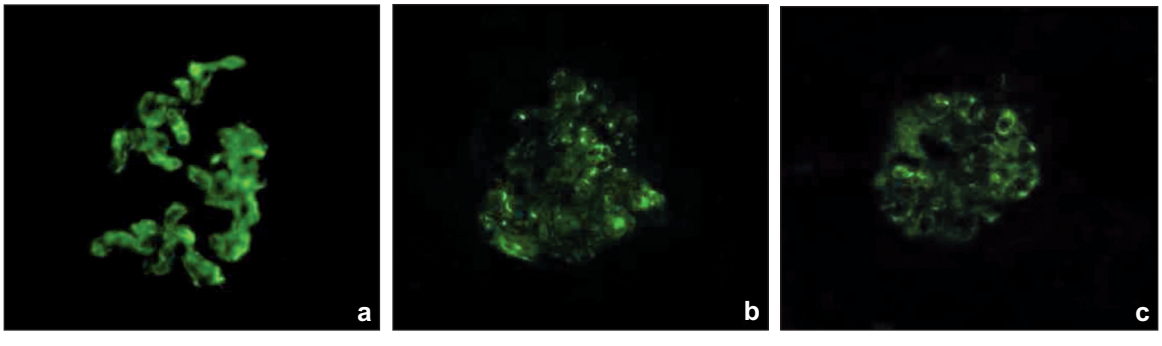

FIGURE 2: a) Direct immunofluorescence demonstrating staning for IgM; **b)** Direct immunofluorescence demonstrating staning for C1q; **c)** Direct immunofluorescence demonstrating staning for C3.

Data about the coexistance of SLE and pSS mostly comes from retrospective observational studies that investigated clinical/serological/histological findings of SLE that developed additionally in the course of pSS.[2-7] In these studies the diagnosis of SLE was made based usually on clinical manifestations. The common clinical symptoms found to indicate the development of SLE in course of pSS were synovitis, arthritis, serositis, Raynaud's phenomenon and malar rash. pSS+SLE patients were younger and the proportion of xerostomia and interstitial lung disease was lower than those with pSS alone. Most of the patients developed anti ds DNA antibodes. In these studies the actual rate of LN in pSS patients was not well defined and only minority of glomerulonephritis developed in course of pSS are classified as LN.[7-9] Our patient developed LN without any clinical manifestations of SLE such as arthritis, serositis and Raynaud's phenomenon. Similar to literature data, the onset age of pSS in our patient was relatively younger than expected average age of onset of pSS.

Studies which comprehensively evaluated pSS alone and SLE+SS have revealed that leukopenia, lymphopenia, proteinuria, and low complement levels could be possible risk factors of pSS that predict development of SLE on pSS.[3-6] Hypocomplementemia in association with HT and nephritic urinary was found in our patient. Given the possibility of drop in complement levels due to polyclonal or monoclonal B cell activation in the course of pSS at a rate of 11%, it is necessary to determine whether a newly developed laboratory findings were a consequence of pSS or is due to concomitant SLE.[10] Despite the absence of anti-dsDNA and typical clinical findings of SLE at the time of renal biopsy, we refer to our case as LN according to revised SLE classification criterias. The anti-ds DNA is considered a specific marker for SLE with high specificity (97.4%) but low sensitivity (57.3%) and often precedes the renal disease exacerbation in SLE. In the literature, a percentage of SLE patients, result negative for anti-dsDNA, is reported to be between 2 to 30%.[9] Our patient was classified in this particular group.

After an immunsupressive treatment we achieved a complete remission with normal C3 levels in our patient. C4 remained low for more that 9 months and this may indicate the possibility of genetic deficiency of early components from classical pathway which is strongly associated with SLE.[10]

This case illustrates the importance of closely follow up of patients with low complement levels and proteinuria developed in the course of pSS. **The awareness of these factors may contribute to early identification of individuals at risk of comorbid renal condition of SLE that may occur in course of pSS.**

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Gülay Koçak, Aylia Yeşilova, Müge Bilge, Münevver Gül Avşar, Fetin Rüştü Yıldız;* ***Design:*** *Aylia Yeşilova, Müge Bilge, Münevver Gül Avşar;* ***Control/Supervision:*** *Müge Bilge, Aylia Yeşilova, Münevver Gül Avşar, Gülay Koçak, Fetin Rüştü Yıldız;* ***Data Collection and/or Processing:*** *Aylia Yeşilova, Münevver Gül Avşar, Müge Bilge, Gülay Koçak, Fetin Rüştü Yıldız;* ***Analysis and/or Interpretation:*** *Aylia Yeşilova, Müge Bilge, Münevver Gül Avşar, Gülay Koçak, Fetin Rüştü Yıldız;* ***Literature Review:*** *Aylia Yeşilova, Gülay Koçak, Müge Bilge, Münevver Gül Avşar, Fetin Rüştü Yıldız;* ***Writing the Article:*** *Gülay Koçak, Aylia Yeşilova, Münevver Gül Avşar, Müge Bilge;****Critical Review:*** *Gülay Koçak, Aylia Yeşilova, Münevver Gül Avşar, Müge Bilge, Fetin Rüştü Yıldız;* ***References and Fundings:*** *Müge Bilge, Münevver Gül Avşar, Fetin Rüştü Yıldız, Gülay Koçak;* ***Materials:*** *Müge Bilge, Münevver Gül Avşar, Gülay Koçak, Fetin Rüştü Yıldız.*

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